41. (new) The ß-cell of claim 39 wherein the inhibitor of IL-1 β is an NF-Kß inhibitor protein.

42. (new) The ß-cell of claim 39 wherein the inhibitor of IL-1 β is an insulin like growth factor-1 protein.---

REMARKS

Claims 1-12, 21-24 and 27-30 are currently pending. The pending claims are rejected under 35 U.S.C. §§112, 102 and 103. For reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

1. The Drawing Rejections

The Examiner has requested that the drawing objections noted in form PTO 948 mailed on 1/4/2000 be corrected. In response, Applicants submit herewith a corrected set of drawings.

2. The Rejections Under 35 U.S.C. §112

Claims 1, 5-7, 21-24 and 27-30 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

According to the Examiner, the claims are drawn to a method of reducing ***any*** ß-cell dysfunction by administering any inhibitor of IL-lß activity. The Examiner maintains that although the intended use of the claimed method is for treatment as it relates to dysfunctional insulin production, the claims are not so limited.

Applicants have amended the claims to indicate that the claimed methods relate to reducing ß-cell dysfunction in an individual with a pancreatic disorder ***wherein said ß-cell dysfunction results in diabetes***.

The Examiner maintains that the genus of inhibitors encompassed by the claims includes any molecule encoded by a nucleic acid that can inhibit any activity of IL-lß (e.g., Fas-mediated ß-cell apoptosis) including antisense molecules, dominant negative polypeptides, decoy receptors, transcription factors, etc. According to the Examiner, in the instant case, no common attributes or features possessed by the IL-lß inhibitors have been disclosed, *i.e.*, there is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations.

Applicants assert that the present invention relates to methods of reducing ß-cell dysfunction comprising introduction of a nucleic acid molecule encoding an inhibitor of IL-1ß or FAS mediated apoptosis into a pancreatic ß-cell. As indicated previously, the essential feature of the present invention is based on the discovery that inhibition of IL-1ß activity, or Fas-mediated apoptosis, reduces pancreatic ß-cell dysfunction. The present invention is not related to, nor do the claims encompass, novel inhibitors of IL-1ß activity. Thus, for purposes of the present

invention, any nucleic acid molecule encoding an inhibitor of IL-1ß or FAS mediated apoptosis may be utilized to reduce ß-cell dysfunction.

Further, Applicants have demonstrated in the working examples of the specification that expression of two IL-1ß inhibitors, interleukin-1 receptor antagonist protein (IL-IRa) and human insulin-like growth factor-I (IGF-1), are capable of reducing ß-cell dysfunction and/or apoptosis. Moreover, the specification clearly teaches one skilled in the art that such inhibitors can be identified by their ability to (i) inhibit insulin release from ß-cells in the presence of IL-1ß and/or (ii) their ability to inhibit nitric oxide production in the presence of IL-1ß. Given the teaching of such distinguishing characteristics associated with the genus of IL-1ß inhibitors, one skilled in the art could determine whether a given composition functions as an IL-1ß inhibitor.

Claims 1-12, 21-24 and 27-30 are rejected under 35 U.S.C.§112, first paragraph. According to the Examiner, the specification does not provide enablement for reducing ß-cell dysfunction, including Fas-mediated apoptosis, by general delivery of a therapeutic nucleic acid to ß-cells *in vivo*. It is further pointed out by the Examiner, that the claims do not indicate that the transfected ß-cells are transplanted into a subject; therefore, the claims are limited to only *in vitro* and *in vivo* embodiments. It is noted that based on the specification and declaration, an essential feature of the invention is that the mammalian ß-cell is isolated, transfected and transplanted in order to practice the claimed invention. Therefore, the invention is only enabled for the method and cell wherein the mammalian cell is an isolated mammalian ß-cell.

Applicants have amended the claims to encompass methods for reducing ß-cell dysfunction wherein nucleic acid molecules encoding either an inhibitor of IL-1ß or Fas

mediated apoptosis are introduced into a ß-cell and said cell is then transplanted into an individual.

Claims 5-8 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, method claims require an active or positive step that accomplishes the goals, however, the instant claims lack such a step.

As indicated above, Applicants have amended the claims to include a step wherein the a ß-cells of step (a) are transplanted into an individual.

Claims 9-12 are said to be indefinite because it is unclear if the method reduces dysfunction of the ß cell comprising the nucleic acid, or if the method reduces the dysfunction of a different ß-cell.

Applicants have amended the claims to indicate that the mammalian ß-cell comprising the recombinant nucleic acid molecule is the cell with reduced dysfunction.

Claims 23 and 24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite because they depend on claim 20. Rejected claims 23 and 24 have been cancelled, without prejudice.

For reasons enumerated above, the rejections under 35 U.S.C.§112, first and second paragraph, should be withdrawn.

3. The Rejections Under 35 U.S.C. §102(b)

Claims 1, 5, 8, 9 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (1996, Human Gene Therapy 7:1719-1726;"Liu"). According to the Examiner, Liu teaches a replication defective HSV-1 vector comprising an inhibitor of IL-1ß activity, *i.e.*, Bcl-2 and the use of such a vector to inhibit cytokine-induced apoptosis. The Examiner maintains that Liu specifically teaches that IL-1ß, IFN-gamma, and TNF-alpha were used in combination to induce apoptosis and cells transfected with HSV-1/Bcl-2 had reduced apoptosis.

An anticipating reference must describe the patented subject with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention. *ATD Corp. v. Lydall, Inc.* 159 F.3d 534 (Fed. Cir. 1998).

The present invention relates to (i) methods for reducing ß-cell dysfunction in an individual with a pancreatic disorder comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1β into a β cell; and (ii) methods for reducing Fas mediated ß-cell apoptosis in an individual with a pancreatic disorder comprising introducing a nucleic acid molecule encoding an inhibitor of Fas mediated apoptosis into a β cell.

Applicants maintain that Liu fails to describe the invention covered by the presently pending claims. Liu merely presents data indicating that expression of bcl2 prevents death induced by a ***mixture*** of cytokines including IL-1β, TNF-α and IFN-γ. Thus, the inhibition of cell death observed by Liu could be due to inhibition of either IL-1β, TNF-α ***or*** IFN-γ cytokine activity. Such data does not teach that inhibition of IL-1 β activity or reduction in Fas mediated ß-cell apoptosis would result in a decrease in ß-cell dysfunction. Therefore, the

claimed invention is not anticipated by Liu, and the rejection under 35 U.S.C.§102 should be withdrawn.

4. The Rejections Under 35 U.S.C. §103

Claims 1, 5, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Human Gene Therapy 7:1719-1726; 1996) in view of Yamabe et al. (BBRC 243:217-223; February, 1998).

According to the Examiner, Liu teaches a replication defective HSV-1 vector comprising an inhibitor of IL-1ß activity, and a mammalian cell comprising the HSV-1 vector which comprises and expresses Bcl-2. The Examiner alleges that, although Liu does not explicitly teach that the nucleic acid can be directly delivered to mammalian ß-cells *in vivo* for the reduction of ß-cell apoptosis, Yamabe teaches a method of preventing hypoxic liver cell necrosis by directly delivering a vector comprising a nucleic acid which encodes and expresses human Bcl-2 protein to an *in vivo* rat liver cell. The Examiner maintains that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Liu and Yamabe and create a method of reducing ß-cell dysfunction *in vivo*, by directly administering a nucleic acid encoding bcl-2 to mammalian beta-cells *in vivo*.

As indicated above, Liu fails to disclose that inhibition of IL-1 β activity or reduction in Fas mediated ß-cell apoptosis results in a decrease in ß-cell dysfunction. Liu merely presents data indicating that expression of bcl2 prevents death induced by a ***mixture*** of cytokines including IL-1β, TNF-α and IFN-γ. Thus, the inhibition of cell death observed by Liu could be due to inhibition of either IL-1β, TNF-α ***or*** IFN-γ cytokine activity. Furthermore, Yamabe fails

to provide the teaching, or suggestion, which is missing from the Liu reference to render the presently claimed invention obvious. Yamabe merely teaches a method of preventing hypoxic ***liver cell necrosis*** by directly delivering a vector comprising a nucleic acid which encodes and expresses human Bcl-2 protein to an *in vivo* rat liver cell. Therefore, the claimed invention can not be rendered obvious in view of Liu and Yamabe, and the rejection under 35 U.S.C. §103(a) should be withdrawn.

Claims 27 and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Welling et al. (1996, Human Gene Therapy 7:1795-1802;"Welling") in view of Amalfitano et al. (1998, J. Virol. 72:926-933;"Amalfitano"). Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Welling in view of Parks et al. (1996, Proc. Natl. Acad. Sci USA 93:13565-13570;"Parks"). Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welling in view of Kadan et al. (1996,WO 96/18414,"Kadan"). Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Welling in view of Liu. Claims 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welling in view of Koeberl et al. (1997, Proc. Natl. Acad. Sci USA 94:1426-1431;"Koeberl"). Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Welling in view of Naldini et al. (1996, Proc. Natl. Acad. Sci USA 93:11382-11388; 1996).

To expedite the allowance of claims, Applicants have canceled claims directed to recombinant vectors without prejudice to their right to prosecute such claims in a later filed continuation application.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Attached hereto as APPENDIX A is a marked-up version of the changes made to the claims by the current amendment. Applicants believe that the invention described and defined by the amended claims is patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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IN THE CLAIMS

Cancel claims 1-12, 21-24 and 27-30, without prejudice.

Please insert the following new claims:

---31. (new)A method for reducing ß-cell dysfunction in an individual with a pancreatic disorder, wherein said dysfunction results in diabetes, comprising:

(i) introducing a nucleic acid molecule encoding an inhibitor of IL-1 β into a β cell; and

(ii) transplanting the β cell of step (a) into the individual so as to reduce β cell dysfunction.

32. (new) The method of claim 31 wherein the inhibitor of IL-1 β activity is an interleukin-1 receptor antagonist protein.

33. (new) The method of claim 31 wherein the inhibitor of IL-1 β activity is an NF-kß inhibitor.

34. (new) The method of claim 31 wherein the inhibitor of IL-1 β is an insulin like growth factor-1.

35. (new) A method for reducing Fas mediated ß-cell apoptosis in an individual with a pancreatic disorder, wherein said apoptosis results in diabetes, comprising:

(i) introducing a nucleic acid molecule encoding an inhibitor of Fas mediated apoptosis into a β cell; and

(ii) transplanting the β cell of step (a) into the individual so as to reduce β cell apoptosis.

36. (new) The method of claim 35 wherein the inhibitor of Fas mediated apoptosis is an dominant negative mutant of the Fas protein.

37. (new) The method of claim 35 wherein the inhibitor of Fas mediated apoptosis is a dominant negative mutant of the FADD protein.

38. (new) The method of claim 35 wherein the inhibitor of Fas mediated apoptosis is a member of the bcl-2 protein family.

39. (new) A mammalian ß-cell comprising a recombinant nucleic acid molecule, said nucleic acid molecule comprising and expressing an inhibitor of IL-1 β activity, wherein the expression of the inhibitor of IL-1 β activity reduces said β cell dysfunction.

40. (new) The ß-cell of claim 39 wherein the inhibitor of IL-1 β activity is an interleukin-1 receptor antagonist protein.

41. (new) The ß-cell of claim 39 wherein the inhibitor of IL-1 β is an NF-Kß inhibitor protein.

42. (new) The ß-cell of claim 39 wherein the inhibitor of IL-1 β is an insulin like growth factor-1 protein.---